Articles for Discussion


Background: This study presents a detailed clinical radiologic surgical and pathologic assessment of early-stage ADCA to determine whether there is a statistically significant correlation between histology and survival among patients with the diagnosis of “AIS” or minimally invasive adenocarcinoma.

Methods: Search of MD Anderson files for stage 1 ADCA with surgical resection and staging:
- 0.5-3.0 cm in diameter
- All resections were reevaluated along with histologic growth pattern.
- 248 cases were identified but only 104 patients were finally selected who were T1N0M0.
- Clinical features, radiologic parameters, and pathology were all collated or reexamined, respectively. Fairly complex statistical analysis was performed (not all of which I understand, “step-wise, backward elimination” being one of them).
- Resected tumors were classified into “conventional categories” of well, moderate, and poorly differentiated based on architecture, nuclear atypia and mitotic activity and % lepidic.

Results: None of the clinical parameters studied showed statistical significance except for the presence of associated malignancies, which negatively impacted survival (p=0.049). This includes whether patients were treated with lobectomy or wedge resection/segmentectomy (p=0.599).

Review of preop CTs in 100/104 patients showed solid, 49; partly solid, 47; and 6, pure ground glass (unfortunately, I don’t see any information regarding how these correlated with pathology).
- No statistical difference determined in outcome based on conventional differentiation in univariate (p=0.105) or multivariate (p=0.125) analysis.
- Tumors further subdivided into two groups, 1 (those showing lepidic growth) and 2 (those with no lepidic growth). Lepidic growth component further subcategorized into those with
  - < 25% lepidic (n=10), 25-50% lepidic (n=11), > 50% lepidic (n=38) OR
  - ≤ 50% for those lepidic (n=21); > 50% lepidic (n=38)
- No statistical significance was encountered between tumors with ≤ 50% or > 50% lepidic component in univariate or multivariate analysis (p=0.121, 0.834, respectively).

“It is evident from Table 2 that even when the initial statistical cutoff p value of < 0.25 was lowered to 0.125, only tumor differentiation met the requirement for multivariable analysis as the percentage of the lepidic component did not converge into the final step, as this variable maintained a p value of 0.835. Nevertheless, we still proceeded to analyze these tumors differently. None of these tumors fulfilled criteria of MIA.” Does anyone know that this means?

Authors then separated out patients in whom there was another associated malignancy (48) from those who did not (56). Lepidic components characterized as follows:
- < 25% (5); 25-50% (3); > 50% (19), all tumors in this group were pure lepidic/AIS OR
- < 50% (8); > 50% (19), all 100% lepidic/AIS
• No difference in survival between cases showing 0 or < 50% lepidic to those with AIS (0.262). In Kaplan Meier statistics no lepidic vs. different proportions of lepidic showed there was an initial trend towards better survival, although not statistically significant for cases with any lepidic component vs. those without (p=0.058). But when tumors with lepidic component were separated by specific percentages there was no statistical difference between the three groups, nor when divided into two groups or even for tumors with pure lepidic pattern (so called adenocarcinoma in situ).

**Discussion:** Patients without a prior history of malignancy did statistically better than those without (p=0.049), but the percentage of lepidic component or tumor differentiation were not statistically correlated with survival. Therefore, the authors argue tumor differentiation is not a reliable predictor of recurrence. There was a trend towards better prognosis but not statistically significant in all of those tumors with a lepidic component (p=0.58). But the fact that further sub-stratification by proportion of lepidic component was not statistically significant sheds doubt on the validity of this feature as being significant. The authors conclude that terms such as AIS and MIA are premature and may be misleading. They suggest the following:

- “On biopsy adenocarcinoma with lepidic or BAC growth (for tumors > 0.5 cm)
- For resected specimens “adenocarcinoma with lepidic (or BAC growth pattern) with percent lepidic component noted
- Size
- Status of pleural integrity
- Status of lymph nodes

**Comment:** It is not clear to me why, if they were trying to determine the significance of the histologic patterns in this case, that they excluded patients who had higher stage disease. I would be very interested in knowing if any patients with AIS, for example, or minimally invasive adenocarcinoma had nodal disease but they excluded those patients from their analysis.


See Excel Spreadsheet


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Neoplasms


Take home message: This is a study in which patients were staged clinically and selected (not randomized) for either segmentectomy or lobectomy. Recurrence free and overall survival were not significantly different between patients undergoing lobectomy.

I think the study would have been stronger if patients had been randomized.


Take home message: It is a risk factor analysis for locoregional recurrence, in contrast to the prior study. These authors retrospectively reviewed 328 patients with clinical stage IA NSCLC who underwent segmentectomy or wedge resection. They wanted to determine risk factors for local regional recurrence or poor disease specific survival. Four independent factors of recurrence were identified: wedge resection, microscopic positive surgical margins, visceral pleural invasion and lymphatic permeation. Independent predictors of poor disease specific survival were smoking status, wedge resection, microscopic positive surgical margins, visceral pleural invasion and lymphatic permeation.

Their conclusions are only partially supported by these data. They state “segmentectomy may be useful to achieve negative surgical margin with an appropriate width of margin and should be the first procedure of choice in patients with clinical stage 1A NSCLC being considered for sublobar resection”. Patients with no suspicion of pleural invasion might also be candidates for sublobar resection.


Take home message: The authors utilize a pyrosequencing technique for the identification of EGFR and KRAS mutations. This method of detecting mutations utilizes luminometric rather than electrophoretic methods. They conclude that pyrosequencing is feasible with a high diagnostic success rate and might offer some advantages over standard electrophoretic techniques.


Take home message: The authors developed a horseradish peroxidase-based IHC detection system using a novel non-endogenous hapten 3-hydroxy-2-quinoxaline (HQ) and tyramide, as well as a dual gene protein ALK assay combining a brightfield break apart in situ hybridization ALK assay with another sensitive IHC method using non-endogenous hapten 5-nitro-3-pyrazole. The new HQ tyramide IHC detection system offered readily interpretable staining with substantially greater sensitivity than conventional ALK IHC. The new ALK protein assay allows concurrent visualization of the ALK gene and ALK protein status in single cells allowing for more accurate ALK status determination even in heterogeneous specimens.

This paper is beyond my level of sophistication in the development of IHCs but should be a great resource for those working in this area.


Take home message: The tissue microarray of 227 pulmonary neuroendocrine tumors was utilized to determine the presence of ALK by immunohistochemistry. Focal reactivity was identified in 3% of 69 small cell carcinomas, 1% of 106 large cell neuroendocrine carcinomas but ALK was not expressed in 52 carcinoid tumors. Neither ALK rearrangement nor amplification was observed using FISH and so no somatic mutations were detected in the three ALK positive neuroendocrine carcinomas. The authors speculate that this aberrant expression is probably wild-type ALK and may be a pitfall when implementing sensitive ALK IHC in the molecular diagnosis of lung cancer.


Take home message: The aim of the current study was to investigate the accuracy of ALK IHC on cytologic specimens for NSCLC. Forty-one (41) specimens with ALK FISH were retrospectively analyzed using the monoclonal antibody 5A4. Specimens were enriched for ALK FISH-positive NSCLC. 37.5% of NSCLCs were ALK-positive by IHC, with only one false-positive and false-negative being identified in comparison to the ALK FISH.

The authors conclude that ALK IHC is highly accurate for detecting ALK rearrangements in NSCLCs.


Take home message: The authors used a number of IHC antibodies (vasohibin-1, endoglin, CD31 and nestin) to determine the status of neovascularization in 93 NSCLC. The vasohibin-1/nestin ratio,
representing the degree of vascular maturation in proliferating vessels, was significantly lower in the central portions of adenocarcinoma than squamous carcinoma. The authors speculate that the fact that newly formed blood vessels are less developed in the central portions of squamous carcinoma might account for complications related to antivascular endothelial growth factor therapy.


Take home message: The authors utilized IHC staining with EGFR mutation-specific antibodies of deletion E746-A750 in exon 19 and L858R in exon 21 in a total of 169 cases of lung adenocarcinoma for which predefined mutational status by direct DNA sequencing had been performed. The overall sensitivity specificity positive predictive value and negative predictive value of IHC using the two antibodies in all specimens were 87.7% (80%/94.3%), 99.0% (97.9%/100%), 98.3% (96%/100%), and 92.8% (88.7%/96.6%), respectively.

The authors conclude that IHC with EGFR deletions E746-A750 and L858R mutation is a reliable screening tool for identifying EGFR mutations in both resected and biopsied lung adenocarcinomas.


Take home message: The authors report what they believe is the first report of IgG4-related disease in a 15-year-old boy admitted for hemoptysis. He was found to have an opacity near the left hilum. Diagnosis was established on the basis of an endobronchial biopsy showing greater than 50% IgG4/IgG plasma cells. Initiation of prednisone promptly resulted in resolution of his hemoptysis and a lowering of his serum IgG4 level.

A nicely done case report by our Italian colleagues.


Take home message: The authors analyzed the number of IgG4-positive plasma cells and the IgG4/IgG ratio in 294 NSCLCs using tissue microarray and conventional surgical specimens. In TMAs, 12% of cases had more than 20 IgG4-positive plasma cells/HPF. In surgical specimens, from these cases, 97% of IgG4-positive plasma cell-enriched cases showed obliterative phlebitis or arteritis within or at the periphery of the tumor. Clinically, none of the patients showed symptoms related to IgG4 systemic disease. Interestingly, patients with stage I squamous cell carcinoma, IgG4-enriched stroma had a more favorable prognosis (P=.04).

**Take home message:** Of 133 women with TSC, 101 had chest CT scans reviewed, among whom 48 (47.5%) met criteria for TSC LAM on the initial CT scan. The authors used a limited CT scanning approach by targeting a single screening image at the level of the carina. The diagnosis of LAM was made if patients had three cysts on imaging. The risk of LAM was age dependent rising by about 8% per year such that the prevalence of LAM was 27% in subjects <21 years of age and 81% in subjects >40 years of age. Among asymptomatic patients with LAM, 84% had cysts present on a single image at the level of the carina. Most patients with LAM eventually developed pulmonary symptoms (63%) and 13% died from LAM. Therefore, most women with TSC ultimately develop cystic changes consistent with LAM.


**Take home message:** Case report of a patient with malignant granular cell tumor. The diagnosis of malignancy appears to be based on the presence of nuclear pleomorphism, mitotic activity, and the presence of coagulative necrosis. 1%-2% of all granular cell tumors have been reported to be “malignant”. The images they show, however, are not convincingly malignant. There is no follow-up on this patient in the case report.


**Take home message:** Case report of a patient with metastatic chondrosarcoma. The patient developed tumor thromboemboli which are nicely illustrated.

The article is listed in the post-graduate medical education corner, but this is a pretty obscure topic to say the least!


**Take home message:** The title is appropriately provocative. The authors present two patients with metastatic mesothelioma presenting as primary bone lesions. The authors have assembled a nice table listing the sites of metastases from malignant mesothelioma, which may be useful and is worth a perusal.


**Take home message:** The article uses lung carcinoma as a test tumor to describe the process of developing cancer data sets which can result in a set of required and recommended data elements and
preferred terminology to be used in the reports. One might wonder why an article like this is necessary but the authors argue that it is necessary because of the growing need to develop consistent data sets across the world. How these international data sets will ultimately merge with the CAP protocols is not entirely clear but I suspect that they will be congruent in the very near future.


Take home message: The authors review 23 cases of spindle cell thymomas (WHO type A), generally thought to have an excellent prognosis. Although the authors state that they are “benign tumors.” I am still not sure about this and as they highlight recent studies, and they document the presence of aggressive behavior and local recurrences in such tumors as well extra thoracic metastases, making me wonder why they state this.

The presence of necrosis correlated with relapse and extrathoracic metastases in 23 patients (out of a total of 600 type A thymomas in the authors data base). None of the other clinical or histologic features including size, predominant nuclear shape, nuclear variability, or mitotic activity were correlated with stage at diagnosis, the development of relapse or extrathoracic metastases. The authors commented that histologic atypia is actually fairly common in WHO type A thymomas.

Articles such as this continue to make me a believer in the Suster and Moran approach to diagnosing thymomas.


Take home message: The authors identify 12 cases of thymoma with prominent glandular differentiation. They were identified in 7 spindle cells (WHO type A), 2 mixed spindle and conventional (A+B1), 2 as conventional (B1) and 1 as an atypical thymoma (B3). Distinct glandular differentiation was present in all cases with mucinous features in 4. There were some differences in the type of glandular proliferation associated with the different types of thymomas. The results, however, are a bit confusing in that the authors do not clearly state which IHC stains were present in which components, but they say “the neoplastic epithelial cells of all tumors showed positive staining for CAM5.2, CK5/6, while Pax8 were negative for TTF1, CEA, EMA and calretinin”. However, some of the glands lined by low cuboidal epithelium showed focal reactivity with antibodies to calretinin and EMA.

Knowledge of this entity is important in making an accurate diagnosis on small biopsies. I think it would have been useful, however, had the authors used a broader array of antibodies including such things as TTF1, CDX2, and more clearly delineated which IHC stains were positive with which antibodies.
Non-neoplastic Disease


This case report is under the images section with very nice CT as well as pathology image from a 34-year-old HIV-positive man. The pulmonary nodules can resolve when HIV treatment is commenced but no follow-up was given on this particular patient.


This represents a clinical practice guideline and proposed classification scheme for pediatric diffuse lung disease. It is quite comprehensive as these things tend to be. The authors use the term chILD as a catch-all term for childhood interstitial lung disease. chILD is defined as occurring in infants of less than 2 years with diffuse lung disease in whom common causes of diffuse lung disease have been excluded including cystic fibrosis, ciliary dyskinesias, recurrent aspiration, etc.

This paper represents an indispensable resource for those who see a significant number of pediatric cases or are interested in them.


This study tried to determine the influence of interstitial lung disease on a population of patients with systemic sclerosis (SSc). No pathology is given, the diagnosis having been established on the basis of diffuse parenchymal opacities on chest imaging. Among 64 incident cases and 43 prevalent cases of SSc, ILD occurred in 19 cases with 3 occurring 6 to 24 months prior to diagnosis. PAH was diagnosed in 14 and heart failure in 27. Seventeen patients died with a median survival of 23 years. ILD and PAH were associated with increased risk of death. The incidence of ILD associated with SSc was low but appeared to be a contributing factor to mortality.

Perhaps pathology is irrelevant but I don’t think so. Given the frequency with which such patients aspirate wouldn’t you want to know what the patients actually had on biopsy?

These authors review 177 patients with hypersensitivity pneumonitis and 224 patients with IPF established by multidisciplinary consensus. HRCT scan fibrosis score and radiographic reticulation were independently predicted time to death or lung transplantation. Patients with IPF had worse survival than those with HP at any given degree of radiographic fibrosis (hazard ratio 2.31; P<.01). The combination of auscultatory crackles and radiographic reticulation identified patients with HP who had a particularly poor outcome.

This study is one of the larger to analyze these features and tips the scale in favor of those studies which show that chronic HP with fibrosis has a better prognosis than patients with IPF. The findings, however, highlight the importance of an accurate diagnosis. Interestingly, pathology was only performed on those patients who ultimately had a diagnosis of HP in whom an antigen was not identified.